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Optimum treatment for primary intracranial Ewing sarcoma

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ABSTRACT

Ewing sarcoma (ES) is an aggressive, high-grade neuroectodermal neoplasm that frequently manifests in children and young adults. Although ES without osseous involvement most commonly involves paravertebral regions of the spine, it very rarely presents as a primary intracranial tumor. This report discusses a unique presentation of an adult extraosseous ES arising from the pineal region with extension into the third and fourth ventricles and multiple drop metastases to the spine. This case demonstrates the application of current chemotherapeutic and adjuvant management and offers insight into possible treatment modalities for metastasis in an atypical extraosseous ES involving the brain and spine.

KEYWORDS Chemotherapy; Ewing sarcoma; pineal region tumor; radiation therapy

Ewing sarcoma (ES) is an aggressive neuroectodermal neoplasm that frequently manifests in children and young adults. ES tumors without osseous involvement are currently classified as extraosseous ES and were previously designated as primitive neuroectodermal tumors, World Health Organization grade IV.[1,2] Histopathological identification of extraosseous ES tumors relies on the presence of a balanced translocation involving chromosomes 11 and 22 or 21 and 22. Extraosseous ES cells characteristically display dense expression of gene product MIC-2 membrane protein (CD99).[3] Approaches to the chemotherapeutic treatment, radiation, and overall prognosis are thought to differ greatly between extraosseous ES and other embryonal tumors.[4] Here we present a case of adult extraosseous ES arising from the pineal region with third and fourth ventricular invasion and evidence of leptomeningeal spread.

CASE PRESENTATION

A 37-year-old man with no significant past medical history presented with a 1-month history of dizziness associated with headache, nausea, vomiting, and tinnitus. Magnetic resonance imaging (MRI) of the brain revealed multiple homogenously enhancing masses of the pineal region, third ventricle, and fourth ventricle, with extension into the bilateral foramen of Luschka, interpeduncular cistern, and dorsal pons *(Figure 1a,b)*. MRI of the cervical, thoracic, and lumbar spine revealed multiple enhancing intradural lesions at various levels consistent with drop metastases *(Figure 1c–e)*. Computed tomography of the chest, abdomen, and pelvis was unremarkable. Cerebrospinal fluid analysis was negative for human chorionic gonadotropin, alpha-fetoprotein, alkaline phosphatase, infection, and malignant cytology. The patient underwent stereotactic endoscopic third ventriculostomy with intraventricular tumor biopsy. The tumor tissue consisted of small round blue cells with an increased nuclear to cytoplasmic ratio and high mitotic activity *(Figure 1f,g)*. Fluorescence in situ hybridization analysis reported rearrangement of the *EWSR1* gene at 22q12, and immunohistochemistry reflected CD99 positivity. A final pathology report from the Mayo Clinic revealed ES, World Health Organization grade IV.

The treatment plan consisted of induction with 6 weeks of weekly vincristine infusion with daily adjuvant craniospinal irradiation of 36 Gy in 21 fractions followed by a boost up to 54 Gy to identifiable gross disease. After four cycles of vincristine infusions, the patient developed *Aspergillus* pneumonia and chemotherapy was withdrawn, while the radiotherapy regimen was continued to completion. A 3-month follow-up MRI revealed marked tumor regression with no residual intracranial or cervical enhancing lesions *(Figure 2)*. A 7-month follow-up MRI revealed no disease recurrence *(Figure 3)*.

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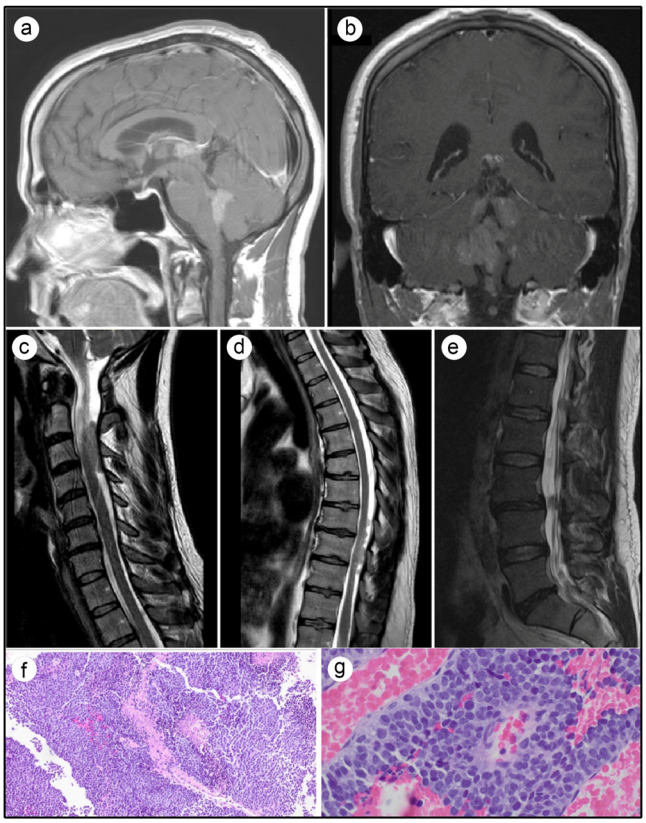

Figure 1. Pretreatment MRI and histology findings. **(a,b)** T1-weighted brain MRI with contrast showing multiple homogenous enhancing masses of the third ventricle and posterior fossa. **(c,d,e)** T2-weighted MRI of cervical, thoracic, and lumbar spines, respectively, showing multiple enhancing intradural lesions at various levels. **(f,g)** Histopathologic features of Ewing sarcoma/peripheral primitive neuroectodermal tumor. Hematoxylin and eosin staining revealed various sheets of small round blue cells with an increased nuclear to cytoplasmic ratio and high mitotic activity.

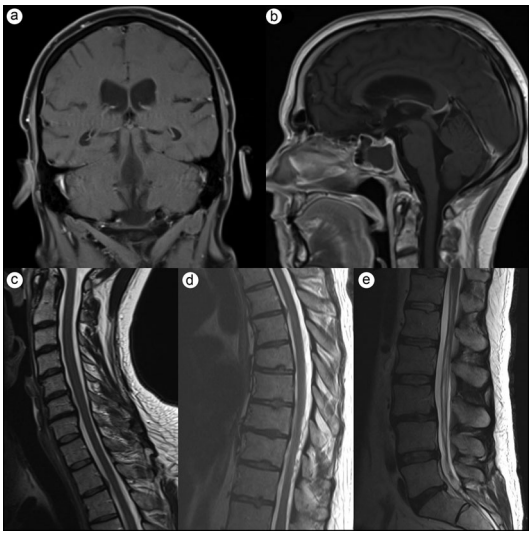

Figure 2. Three-month follow-up T1-weighted brain MRI and T2-weighted spine MRI. **(a,b)** Marked tumor regression with no residual intracranial or **(c)** cervical enhancing lesions. **(d)** One area of minimal enhancement remained in the thoracic spine. **(e)** The lumbar spine was significantly improved with only minor residual thickening of the cauda equina.

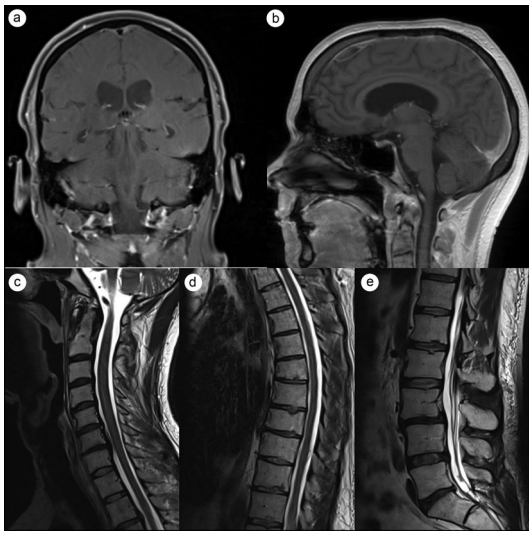

Figure 3. Seven-month follow-up T1-weighted brain MRI and T2-weighted spine MRI. **(a,b)** Stable tumor regression with no residual intracranial lesions. **(c-e)** Marked regression of metastatic spinal lesions with no enhancement in **(d)** thoracic or **(e)** lumbar spine.

DISCUSSION

Due to the rare occurrence of primary intracranial ES, there remains limited evidence regarding optimal management strategies. Although primary intracranial extraosseous ES with leptomeningeal dissemination has been rarely described in the literature, no other cases share the extent of central nervous system metastasis present in this patient.[5–7] Radiation and chemotherapeutic management strategies for primary intracranial ES with metastasis are illustrated in *Table 1*.[5–9]

A study of 14 cases from a single institution revealed that patients who underwent adjuvant radiotherapy had statistically significant improvement in 1- and 2-year survival and median survival time compared to patients without radiotherapy.[6,10] Radiation regimens are typically initiated postoperatively with the standard craniospinal irradiation protocol of 36 Gy in 21 fractions followed by a boost to 54 Gy.[6] In this case, craniospinal irradiation served as the primary method of treatment due to the mid-cycle discontinuation of chemotherapy. This case illustrates how adjuvant radiotherapy is a cornerstone of extraosseous ES treatment, specifically in the context of subtotal resection and/or evidence of metastasis.

The benefit of adjuvant chemotherapy in extraosseous ES treatment remains controversial. In adults, chemotherapy is never used in isolation but rather in combination with resection and/or radiation.[6] However, isolated chemotherapy has been used in pediatric cases when radiation cannot be tolerated.[6,11] Multiagent therapy has largely been utilized in patients with nonresectable or metastatic tumors. The current regimen for ES includes vincristine, doxorubicin, cyclophosphamide, and dactinomycin alternating with ifosfamide and etoposide.[12,13] This multiagent therapy has shown

Table 1. Management of primary intracranial Ewing sarcoma with metastasis

Author, year	Age/sex	Tumor location	Location of metastasis	Resection	Radiation (Gy)	Chemotherapy regimen	Follow-up (mo)
Present case, 2020	37, M	Pineal region	Spinal cord	Biopsy	36	4 weeks vincristine	No disease (7)
Chen et al, 2018[6]	23, M	L TP, DB	Spinal cord	STR	55	None	Died (6)
Chen et al, 2018[6]	22, F	R T	Skull	GTR	55	VAC	Died (38)
Chen et al, 2018[6]	12, F	R T, L FP, DB	Diffuse metastasis	STR	50	VIDE	Died (20)
Alqahtani et al, 2017[7]	3, M	PF	Spinal cord	GTR	NS	VIDE + C for 3 mo then VTI	Recurrence (8)
Tanboon et al, 2012[8]	22, F	Frontal DB	Diffuse metastasis	GTR	None	None	Died (6 postop)
Mobley et al, 2006[9]	21, M	O	Multiple vertebrae	Biopsy	54	Dactinomycin, VAC	Recurrence (18)
Jay et al, 1996[5]	4, M	PF	Spinal cord	GTR	CSI, dose NS	VCE then ICE	Progression of LMS

CSI indicates craniospinal irradiation; DB, dural-based; F, frontal; FP, frontoparietal; GTR, gross total resection; ICE, ifosfamide, carboplatin, etoposide, mesna; L, left; LMS, leptomeningeal spread; NS, not specified; O, occiput; PF, posterior fossa; R, right; STR, subtotal resection; T, temporal; TP, temporoparietal; VAC, vincristine, doxorubicin, cyclophosphamide; VCE, vincristine, cyclophosphamide, epirubicin; VIDE + C, vincristine, ifosfamide, doxorubicin, etoposide plus cyclophosphamide; VIDE, vincristine, ifosfamide, doxorubicin, etoposide; VTI, vincristine, temozolomide, irinotecan.

great efficacy in the treatment of ES of bone; however, its application to intracranial extraosseous ES remains unclear. In the case presented, the chemotherapeutic regimen was largely based on the medulloblastoma protocol known as the "Packer protocol": vincristine weekly for 6 weeks during radiation, then 6 cycles of cisplatin, cyclophosphamide, and vincristine every 28 days.[14] In patients with primary intracranial ES, the efficacy of ES vs medulloblastoma protocols has yet to be investigated. This patient did not complete the induction-phase regimen but showed marked tumor regression without recurrence after 7 months with radiotherapy alone. Therefore, the full benefits of chemotherapy as an adjuvant therapy remain unproven in this patient.

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